ferred solvent for NP-59, although should this problem become more frequent in the future, the difficulty of accurately resolving a radiocholesterol colloid from NP-59 could negate this usefulness in favor of a more desirable solvent system.

HANK CHILTON
JON C. LEWIS
STEVEN F. MOTSINGER
ROBERT J. COWAN
Bowman Gray School of Medicine
Winston-Salem, North Carolina

FOOTNOTE

* Lot No. 061378NP5975, University of Michigan Nuclear Pharmacy, Ann Arbor, MI.

REFERENCES

1. VIVIAN A, ICE RD, SHEN V, et al: Radiochemical Purity of Radiopharmaceuticals Using Gelman Seprachrom Chromatography, Gelman Instrument Co., Ann Arbor, 1977
2. ZIMMER AM, DAVEL DG: Rapid miniaturized chromatographic quality control procedures for iodinated radiopharmaceuticals. *Am J Hosp Pharm* 35: 426–428, 1978

## Altered Biodistribution of 6β-[$^{131}$I]-Iodomethyl-19-Norcholesterol (NP-59): Radiopharmaceutical Contamination or Patient Idiosyncracy?

The University of Michigan Nuclear Pharmacy is naturally concerned with any reported problem in regard to the use of NP-59. Although we do not question the obviously abnormal biodistribution observed in the reported study, we are not totally convinced that this phenomenon was due to the presence of an insoluble colloidal contaminant in our original formulation.

In the manufacturing sequence of NP-59, an initial step involves the preparation of 10-mCi multiple-dose vials. These 10-mCi "bulk" vials are subsequently subdivided into five 2-mCi individual dose vials. Our followup conversation with each of the four other investigators who received *exactly* the same material from the same "bulk" vial as this investigator revealed no altered biodistribution patterns. We have received no other reports of problems with this batch of NP-59 (061378NP5975), nor did we observe reticuloendothelial uptake in four patients studied with the same material at our institution (Fig. 1).

**FIG. 1.** Posterior scintillation image (computer display) obtained in a Cushingnoid patient 5 days after administration of 1 mCi of NP-59 (Lot No. 061378NP5975).

Regarding the apparent demonstration of spherical particles in the electron micrographs, we note that the Tween-80 surfactant used in the formulation most likely exerts its solubilization effects on NP-59 via micellization. Micelles (association colloids) are spherical aggregates of colloidal dimensions, not to be confused with insoluble colloids routinely encountered in radiopharmaceutical preparations. This phenomenon would not only explain the presence of the uniform spherical particles, but also their ultrastructural similarity to a naturally occurring association colloid, the plasma lipoproteins (*1*).

If an *insoluble* colloidal impurity were present in this preparation of NP-59, one would have expected to visualize it at an $R_f$ of 0.0 using an instant thin layer chromatography (ITLC) silica-gel: normal-saline system. Although your correspondents did not observe the presence of this impurity in their initial analysis, we agree that it may be difficult to separate its $R_f$ peak from the $R_f$ of NP-59 (0.15). On the other hand, they state that further in vitro analysis (ITLC silica-gel: analytical-grade chloroform) showed the presence of a colloid-like radiochemical impurity at an $R_f$ of 0.8, which was in contrast to that reported for NP-59 (0.6). Careful inspection of the sample chromatogram presented in their reference for this chromatography system reveals that the $R_f$ of 19-[$^{131}$I]-iodocholesterol is 0.6, with the $R_f$ of NP-59 being somewhat higher (*2*). Our experience in the use of an ITLC silica-gel: chloroform system for the radiochemical analysis of NP-59 has been unsatisfactory, with considerable spreading of the radioactive peak; therefore we have recommended (*3*), and continue to recommend, the use of Thin-Layer Chromatography (TLC) silica-gel: analytical-grade chloroform ($R_f$ of NP-59 = 0.4).

Another tenable explanation for the observed altered distribution of NP-59 is patient idiosyncracy. Although we have not witnessed such a pattern in over 200 patients studied at the University of Michigan, the relative lack of overall clinical experience with NP-59 leaves this as one possibility. Patient history, including laboratory values and current drug therapy (i.e., corticosteroids), is required to evaluate such a possibility and is, in fact, of paramount importance to the interpretation of any adrenal scintigraphic study.

In summary, the altered biodistribution of NP-59 reported may be a result of an insoluble radiochemical impurity in the preparation, or a patient idiosyncracy. Our followup analyses on this batch of NP-59 indicates that a radiocolloid contaminant was probably not present in the original formulation. We do recognize the possibility for radiochemical impurity formation as a result of the rigors of shipment or on-site manipulation of the agent, and therefore stress the importance of quality control by each investigator. However, we don't feel that the results of the quality control tests presented in the letter in question definitely indicate the presence of a colloidal impurity in the preparation, either before or after administration. Further analysis of this patient's history is necessary to evaluate properly the possibility of a patient idiosyncracy.

DENNIS P. SWANSON
NANCY E. WIRTH
MILTON D. GROSS
University of Michigan Medical Center
Ann Arbor, Michigan

REFERENCES

1. ELWORTHY PH, FLORENCE AT, MACFARLANE CB: *Solubilization by Surface-Active Agents*. Bungary, Suffolk, Great Britain, The Chaucer Press Ltd., 1968, pp 13-60
2. VIVIAN A, ICE RD, SHEN V, et al: *Radiochemical Purity of Radiopharmaceuticals Using Gelman Seprachrom Chromatography*, Ann Arbor, MI, Gelman Instrument Co., 1977, p 23

3. BEIERWALTES WH, WIELAND DM, YU T, et al: Adrenal imaging agents: Rationale, synthesis, formulation, and metabolism. *Semin Nucl Med* 8: 5-21, 1978

## Reply

We appreciate the concern of the Swanson group that a patient idiosyncracy could be responsible for the altered biodistribution of NP-59 that we recently reported (*1*). Initially, we recognized this possibility and, before performing electron microscopy on that particular lot of NP-59, we reviewed the patient's clinical and drug history to rule out such an occurrence. We could not find any events in the history that we felt were remarkable. The patient, a 57-year-old woman, had a previous history of hypercalcemia and hypokalemia and was admitted to our hospital for evaluation in June of 1978, after being hospitalized twice in a nearby city over the preceding 7-mo period. Upon each admission the patient complained of weight loss, decreased appetite, and malaise. During hospitalization, she was treated with oral potassium supplements, her symptoms abated, and she was subsequently discharged. Soon afterward, her symptoms returned and she was readmitted. When admitted to our hospital, the patient's electrolytes were within normal limits except for potassium (2.1), phosphate (2.2), uric acid (9.5), and calcium (12.7). While hospitalized her serum calcium was persistently elevated and serum phosphate was low. A diagnosis of hyperparathyroid adenoma was surgically confirmed on June 7, 1978. Because it had been suggested that she could have a multiple adenomatous syndrome (in regard to her profound hypokalemia before surgery), the patient was scheduled to return as an out-patient on June 19 for an NP-59 adrenal study. At the time of her discharge from our hospital, she was placed on Darvocet-N, Quinamm, Slow-K tablets, and Lugol's solution (beginning 2 days before adrenal imaging).

We recently obtained a newer lot of NP-59 (Lot No. 120578NP5986, vial S-6) for adrenal imaging in another patient. In the original communication, transmission and scanning electron microscopy revealed the presence of large spherical particles in NP-59 (Lot No. 061378NP5975). We suspected that the RES uptake of NP-59 in that particular patient was due to the presence of these colloid-like particles. The manufacturer of NP-59 states, however, that the use of the surfactant, Tween-80, during preparation of NP-59 probably results in micellization, which would account for our finding, in NP-59, of particles having colloidal dimensions (Fig. 1). We note that the particles observed in our most recent lot of NP-59 have diameters in the range of 15-30 nm (Fig. 2), which is significantly smaller than those particles with diameters in the 200–300 nm range that we observed with the earlier NP-59 preparation. Likewise, scintiphotos obtained with the newer lot of NP-59 failed to demonstrate any RES distribution. It is conceivable that these smaller particles, which may be characteristic of NP-59, had in the earlier preparation coalesced to form the larger spheres that we observed. Such an occurrence would explain our electron microscopy findings and the subsequent RES distribution of the NP-59 in our patient.

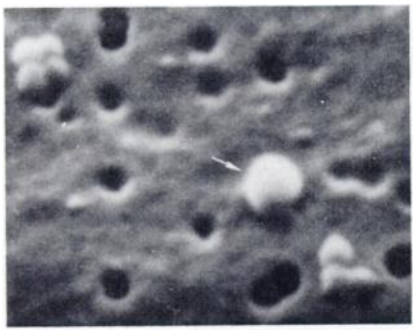

**FIG. 1.** Electron micrograph of earlier NP-59 preparation (Lot No. 061378NP5975) which produced RES uptake. Scanning micrograph on filter membrane, × 50,000, shows large particles (arrow) in range of 200-300 nm.

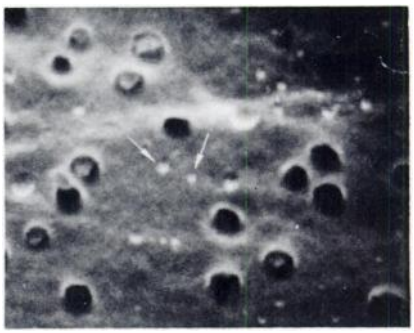

**FIG. 2.** Newer lot of NP-59 (Lot No. 120578NP5986, vial S-6) shown in scanning electron micrograph on filter membrane, × 50,000. Particles (arrows) in the 15-30 nm range are seen; they are significantly smaller than those observed in the earlier NP-59 preparation.

HANK CHILTON
JON C. LEWIS
STEPHEN F. MOTSINGER
ROBERT J. COWAN
Bowman Gray School of Medicine
Winston-Salem, North Carolina

REFERENCE

1. CHILTON H, LEWIS JC, MOTSINGER SF, et al: Reticuloendothelial Distribution of a Colloid-Like Material In 6β-[$^{131}$I]iodomethyl-19-norcholesterol (NP-59). *J Nucl Med* 20: 803-805, 1979

## Transmission Computerized Tomography and Serial Scintigraphy in Intracranial Tumors: What is the Desirable State of the Art?

The radionuclide methods we have used for the comparative study (*1*) have been described as less than "state of the art" (*2*). Our methods did not, in fact, routinely include the vertex view and radiopharmaceuticals like DTPA or glucoheptonate, but they were good enough to detect 91% of 215 intracranial tumors and 189 of 204 patients with such tumors. Moreover, they were sufficient to detect 93.1% of completed ischemic stroke and 77.3% of patients with transient ischemic attack or prolonged reversible ischemic neurologic deficit (*3*). None of the undetected tumors in our study (*1*) would have been detected by vertex-view imaging because all such tumors were either close to the base of the skull, or measured less than 1 cm in diameter, or did not take up [$^{99m}$Tc] pertechnetate because of histologic type (grade-1 glioma etc).

In our opinion it is not necessary to improve the static (early and late) parts of cerebral serial scintigraphy (CSS), as proposed by Daly (*2*), because a) delayed images are useful only if metas-